REMARKS/ARGUMENTS

The Status of the Claims.

Claims 1-46 are pending with entry of this amendment, no claims being cancelled. Claims 28, 29 and 36 to 46 are currently under consideration, while claims 1-27 and 30-35, not elected in a prior restriction action, have been withdrawn Claims 28 and 29 are amended herein. Claims 36 to 46 are new. These amendments introduce no new matter and support is replete throughout the specification. These amendments are made without prejudice and are not to be construed as abandonment of the previously claimed subject matter or agreement with any objection or rejection of record.

With respect to claims 28 and 29, the amendments merely exchange "is" and "are" language with "comprising" language. These methods claims are also amended to incorporate essentially the limitations of withdrawn claim 1.

With respect to new claims 36 to 46, they are essentially copied from original claims 2 to 5 and 7 to 13, but in a form dependent from claims 28 and 29. These claims were added to essentially retain the relationship between methods claims 28 and 29, and original composition claims 1 to 5 and 7 to 13, which have been withdrawn from consideration.

Applicants submit that no new matter has been added to the application by way of the above amendments. Accordingly, entry of the Amendment is respectfully requested.

35 U.S.C. §112, Second Paragraph.

Claims 28 and 29 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for alleged failure to particularly point out and distinctly claim the invention.

The Examiner has suggested that because claim 13 (now essentially copied as new claim 46) is directed to a single nucleobase compound of formula VI, it is unclear how the this compound can be a nucleic acid binding compound of either independent claim 28 or

claim 29. In order to eliminate any confusion, Applicants have amended claims 28 and 29 to replace the words "is" and "are" with comprising language. With this language, it is clear that a nucleic acid binding compounds can comprise a formula VI nucleobase of new claim 46.

Claim 29 has further been rejected under section 112, second paragraph, based on the alleged indefiniteness concerning what is meant by the term "disintegrating the probe". The Examiner alleges it is unclear whether the disintegration is chemical or enzymatic. Although the disintegration can optionally be by chemical and/or enzymatic reactions, the claim is currently amended to focus on the embodiment of disintegration of the probe by an enzymatic activity. With this amendment, it is clear that the currently claimed probe disintegration is the result of enzymatic activity. Support for the amendment can be found, e.g., in the specification at page 32, line 21.

The Examiner finds it unclear whether the probes are decomposed into single bases or else. Applicants note that they are not required to provide a theory of how the invention works. However, Applicants believe it does not matter, with regard to the claim or function of the invention, whether the probes are decomposed to single bases or not. What is necessary is that the probe be disintegrated (see Webster's: 1 to break or separate into constituent elements or parts) so the reporter groups can be separated. This can occur with a single break in the chain, multiple breaks, or complete digestion of all nucleotides from the chain. This would be clear to one skilled in the art on review of the specification and claim.

Because the claims, as currently amended, are clear and enabled, Applicants respectfully request withdrawal of the rejections under section 112.

35 U.S.C. §103(a).

Claim 28 was rejected under 35 U.S.C. §103(a) as allegedly obvious based on Seela in view of Chollet. Applicants traverse.

Three requirements must be met for a *prima facie* case of obviousness. First, the prior art reference must teach all of the limitations of the claims. M.P.E.P § 2143.03. Second, there must be a motivation to modify the reference or combine the teachings to

produce the claimed invention. M.P.E.P. § 2143.01. Third, a reasonable expectation of success is required. M.P.E.P. § 2143.02. The teaching or suggestion to combine and the expectation of success must be both found in the prior art and not based on Applicants' disclosure. M.P.E.P. §2143.

Specifically, a *prima facie* case of obviousness requires that the combination of the cited art, taken with the general knowledge in the field, must provide all of the elements of the claimed invention. When a rejection depends on a combination of prior art references, there must be some teaching, suggestion or motivation to combine the references. In re Geiger, 815 USPQ2s 1276, 1278 (Fed. Cir. 1987). Moreover, to support an obviousness rejection, the cited references must additionally provide a reasonable expectation of success. In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991), citing In re Dow Chemical Co., 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

The combination of Seela and Chollet does not render the invention obvious for a number of reasons. For example, the combination of references does not provide all limitations of the claims, the combination is not motivated, and one skilled in the art at the time would not have had an expectation of success in the suggested combination.

The cited combination does not disclose all elements of claim 28. Seela monitors hybridization in solution of oligonucleotides substituted with 2-aza-2'-deoxyadenosine. Chollet provides Southern blot hybridizations using ^{32}P-labeled 2-amino analog probes to detect genomic DNA samples bound to a solid support. Seela and Chollet, individually or in combination, fail to provide the limitation of "contacting said sample with a solid phase having immobilized on its surface nucleic acid binding compounds each containing a sequence complementary to one of said particular sequences of said nucleic acids". In a conclusory statement at page 4 of the Office Action, the combination is "viewed to be inclusive of the solid phase having immobilized on its surface the nucleic acid compounds." This statement is unsupported and fails to grasp an important novel and non-obvious aspect of the invention.

The presence of the nucleic acid binding compounds (NABCs) on the solid support, as compared probes in solution in the cited references, is a critical difference over the old art. The ability to adjust two or more NABCs, comprising compounds of the claims

to specifically hybridize or melt at about the same temperature with their complimentary sample sequence, allows, e.g., an array of NABCs on a solid support to screen and identify two or more different sequences in the same sample at the same time under the same hybridization conditions. This cannot be accomplished with any combination of technologies described in Seela and Chollet. For example, hybridization of a solid support bound sample with two or more probes of Chollet would provide ambiguous results. That is, should a detectable signal appear at the solid support location of the sample, one could not tell which probe, or combination of probes, had hybridized to the sample nucleic acid sequence. Because the cited references do not teach all the limitations, claim 28 is not obvious and the section 103 rejection should be withdrawn.

The cited combination is not motivated. Assuming, for the sake of this argument, that all limitations could be found in the references, the unmotivated combination would not render claim 28 obvious. The references do not provide a suggestion to make such a combination. Furthermore, the combination is not motivated because it would render the cited art unsatisfactory for its intended use (see, *In re Gordon*, 733 F.2d 900, 221 USPQ 1125), the combination would change the principle of operation of the primary reference being modified (see, *In re Ratti*, 270 F.2d 810, 123 USPQ 349), and there would not be an expectation of success in the combination.

The Seela probes were intended to be used for melting studies in solution with spectroscopic detection. The Seela probes would no longer be satisfactory for their intended purpose if modified by binding them to a solid support. For example, the presence of the solid support and mandatory blocking agents in a hybridization buffer would change the hybridization kinetics and make spectroscopic detection impossible. The Chollet radioactive labeled probes with nucleotide analogs were intended to detect sample nucleic acid sequences bound to a solid support. The Chollet probes would no longer be satisfactory for this use if they were bound to a solid support. For example, the probes would no longer be able to hybridize with sample sequences bound to a solid support and would provide only useless non-specific signals from their location on the solid support. Therefore, according to *In re Gordon*, the combination is not motivated.

The principle of operation for the oligonucleotides in Seela primary reference is spectrographic detection of absorbance changes as oligonucleotides hybridize and melt in solution to provide melting temperatures and melting profiles. In combination with technology of Chollet, the Seela probes and methods would have to be modified to include radioactive labels and detection methods. Instead of gathering information at or near a Tm, the operation would focus on detection of signals at hybridization stringencies away from the Tm. The principles of operation would be changed and the methods would provide different output results. Again, it should be noted that even with the modifications of the combination, the elements of claim 28 would not be described. The combination of Seela and Chollet is not motivated and the rejection should be withdrawn, according to *In re Ratti.*

There would not be an expectation of success in the combination of Seela and Chollet. With the changed principles of operation and foreseeable unsatisfactory results, described above, one skilled in the art at the time of the invention would not have had an expectation of success for the cited combination. In fact, the combination would fail to provide the invention of claim 28. Expectation of success would be further eroded in the admitted extension errors (page 315) and high background probes (page 310) in Chollet. Moreover, the unexplained and illogical increased melting temperatures of mismatched oligonucleotides presented in Table II suggest to one skilled in the art that the probes and methods of Seela could not be relied on to specifically identify matching target sequences.

Because the combination of Seela and Chollet is unmotivated and fails to provide all the limitations of the claim, they can't render claim 28 obvious. Applicants request withdrawal of the section 103 rejection in this case.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the claims are deemed not to be in condition for allowance after consideration of this Response, a telephone interview with the Examiner is hereby requested. Please telephone the undersigned at (510) 769-3510 to schedule an interview.

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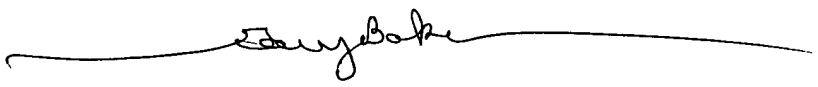
Respectfully submitted,



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Attachments:

1) A transmittal sheet;
2) A fee transmittal;
3) A petition to extend the period of response for 2 months; and,
4) A receipt indication postcard.

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